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EXAMINER	
BERNHARDT, EMILY B	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,653	LE-BRUN ET AL.	
	Examiner	Art Unit	
	Emily Bernhardt	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-14 and 16-21* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicants' election of Group I subject matter with traverse is acknowledged but is not persuasive for the following reasons. Evidence of an art-recognized equivalency teaching is not seen for pyrrole/pyrazole cores covering such an array of permutations as covered by the claims. Note the art cited below does not teach the interchangeability of said azole rings. Applicants' additional comment that the search is not burdensome given that only 2 classes need be searched is inaccurate. Each of class 544 and 546 contains more than 300 subclasses from which various species are ultimately classified. The examiner has given some examples of the differing fields of search. Indeed the request for further restriction indicated in the previous action is necessitated by the many subclasses which would need to be searched when R1 is a heteroaryl. Additionally, differing issues of patentability would be raised by the nature of the compounds when R1 is for example pyridyl. While a pyridyl species has been excluded by proviso which is identified as being within the disclosure of WO'798, said species would be at the very least, structurally similar to methylated analogs which are within the claims' scope. The same would

apply to the teachings of Ermondi also cited in the specification as the reason for the 2nd excluded species, which has for R1 a quinazoline moiety.

Accordingly, the restriction is deemed proper and is therefore made FINAL .

In view of the above differing issues and separate fields of search for aryl vs heteroaryls, Group I has been further restricted as set forth below.

IA. Claims 1-7,9-16 ,drawn to compounds and compositions where R1= aryl and substituted aryl- i.e. aromatic carbocyclic rings.

IB. Claims 1-5,8-14 and 16, drawn to compounds and compositions where R1= heteroaryl and substituted heteroaryl-i.e. at least one hetero ring present.

Applicants' elected species falls within IA. Applicants are advised that the claims will only be examined with respect to Group IA subject matter.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 17-21 are rejected under 35 U.S.C. 101 because

the claimed invention is directed to non-statutory subject matter. Claims drafted in terms of "use" have been held to be nonstatutory. Note

Clinical Products v. Brenner 149 USPQ 475. **These claims will not be further treated on the merits.**

The abstract of the disclosure is objected to because it does not depict the structural makeup of applicants' invention, namely formula (I). Correction is required. See MPEP § 608.01(b).

Claims 1-12 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Nature of "substituted" appearing throughout the R1-R3 and R7,R8 and R12 variables is of unknown scope. Except for the "preferred" embodiments described on p.5 for R1 and R2 remaining scope of "substituted" is unknown and thus applicants' intended scope not clear.

2. There are several instances of "alkylene" appearing as a monovalent moiety in the R3/R4 choices which is open-ended since the term denotes a divalent moiety, for example, $-CH_2-$ and thus while one end is attached to the pyrazole ring or some intervening atom the other end is left with a dangling valence. Also see "cycloalkylene" in the R3 list.

3. Nature of prodrugs in all the claims is not set forth much less location of attachment. Many functional groups are capable at least in theory to being

derivatized but more than minimal experimentation would be required to determine what is and what is not within the instant scope since the choice of a suitable prodrug requires testing for rate of hydrolysis as well as in vivo stability and knowledge of an intended effect (i.e. modification of a undesirable property in the parent drug) and such is a function of the molecular structure of the parent drug as any textbook on prodrugs will confirm. What constitutes a sufficient degree of hydrolysis to be a suitable prodrug ? 95% ? 100% ? Specification provides no guidance.

Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. There are **many** species that are outside the scope of claim 1. See all the species on p.165 and top part of p.166. These compounds have the pyrazole attached to the "L" group at the 4-position not 3-position appearing in the formula of claim 1. The same is seen for 10th and 11th species on p.182. Also for these species are the dimethyl groups on the phenyl ring or on the pyrazole ring? Applicants are advised

to check for remaining elected species within this claim for additional inconsistencies in the nomenclature and/or proper claim dependency.

If this is a typo applicants must clearly demonstrate that any changes to the species is not new matter.

Claim 13 lacks a period after the last species on p.184.

Claim 13 is rejected under 35 U.S.C. 101 because the invention as claimed lacks utility. The species identified in the above objection are not only outside the scope of claim 1 but are also not generically described elsewhere in the specification nor specifically tested. Thus they cannot be ascribed the utilities disclosed for members within the scope of of the instant invention.

Claims 1-7,9-13 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following reasons apply.

1. As the species in claim 13 pointed out above in the par.4 objection and 101 rejection lack utility, there is no teaching how to use such species and thus they fail to comply with par.one enablement requirements.

2. For the remainder of the claims which are generic, there is no reasonable basis for assuming that the myriad of compounds embraced by said claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. The rejection is directed to the scope at all R variables which include "optionally substituted" derivatives of nonlimiting scope as well as to those R variables (R1 and R3) which embrace a variety of functional groups including any heteroaryl, heterocyclic either directly or indirectly attached to the pyrazole ring. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art.

Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition, which includes factors such as:

1) Breadth of the claims- the claims cover compounds easily in the billions based on the permutations pointed out above;

2) Level of unpredictability in the art- the invention is pharmaceutical in nature as it involves the inhibition of tubulin polymerization which involves the binding of a drug to a binding site on tubulin of which there are several. This in turn requires sufficient SAR data to determine if and what type of structural modifications to the basic structure will affect binding site while retaining cytotoxicity. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See In re Fisher 166 USPQ 18. ;

3) Direction or guidance- the compounds made and tested are not representative of the instant scope but are closer to each other than to remaining scope being mainly within the scope of claims 4,9 and 10 **combined** and additionally having C(O) as L;

4) State of the prior art- The compounds are piperazine derivatives attached to pyrazole at the 3-position by way of a variety of linking groups with diverse substitution permitted at most of the R variables. While such compounds are known as evident from the art applied below, they describe a small portion of the compounds claimed herein and thus do not evidence

the many structural permutations permitted in the instant scope are known for at least one use in the prior art;

5) Working examples- While test data has been presented for many compounds, they are very similar in structure to each other and thus no clear evaluation of which unmade, untested functional groups at various positions out of the many claimed might affect potency to a large or small degree.

In view of the above considerations, this rejection is being applied.

Claims 1-7,9-12 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula (I) in the free form or salt form, does not reasonably provide enablement for prodrug forms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Prodrugs as recited in all of the claims reads on any and all such groups (thioesters, lactones,etc.) regardless of complexity of structure and point of attachment to the basic structure for which there is no sufficient teaching how to make and how to use at any one **selective** location among the many possible sites present . Applicants provide no reasonable assurance

that any and all prodrug derivatives of instant compounds will have the ability to generate the instant compounds *in vivo* by one or more processes. Designing prodrugs is far from trivial as any textbook on prodrugs will confirm.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-7,9,10,12 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Gerlach (US'734). The published application describes compounds within the instant scope for use as antitumor agents. See compounds in sections [0052] and [0054] on page 4. Gerlach is applied as of its US filing date of 6/27/03 which precedes applicants' US filing date. The provisional filing date of Gerlach is not being relied on since the

disclosure is much narrower and lacks a description of any one of the pyrazole species relied on herein. It is recognized applicants are also claiming earlier benefit under 35 USC 119(e) which would antedate Gerlach. However, benefit is not being granted since the claims are not completely described in the earlier provisional application. Compare the scope at R2 as well as R3 as well as the substituents permitted on R1 phenyl rings. Also, benefit is not being granted in view of noncompliance with 35 USC 112, par. one for the reasons set forth in the above 112 rejections. Also see MPEP 706.02, section V, part (D).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerlach (US'734). Subject matter covered in these claims is obvious in view of the teachings of Gerlach applied in the above 102 rejection. Claim 11 requires that pyrazole ring be methylated which is also taught by Gerlach. See list of possible substituents which includes alkyl on p.3, right column. There is, additionally, case law that holds H vs

Me on carbon atoms in otherwise identical compounds to be obvious variants absent evidence of superior, unexpected results. See In re Wood 199 USPQ 137; In re Lohr 137 USPQ 548; In re Fauque 121 USPQ 425.

Claim 13 which recites more than 300 species contains at least one species that is also rendered obvious by Gerlach. See last species on p.169 which only differs in being methylated on pyrazole ring as required by claim 11. Additionally, in claim 14 last species on p.184 is an obvious variant since it is a 3,5 dimethoxyphenylpiperazine which is preferred at R1 in Gerlach and additionally methylated on pyrazole. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify the compounds described in Gerlach as pointed out above by methylating the pyrazole ring and modifying the substitution on phenyl ring to 3,5 dimethoxy in view of the equivalency teachings outlined above.

Gerlach is competent for these claims because the subject matter in 11 and 14 is not entirely described in the US provisional case and while for claim 13 it appears all the species drawn to the elected invention are described in earlier priority case, said claim does not comply with 35 USC 112, par.one as discussed above. In response to this rejection, applicants

are requested to state for the record if species still present in this claim are described in the US provisional case.

Applicants are also requested to perfect their 119 foreign priority by furnishing a certified English translation of the French priority document.

Claims 1-7,9-12 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poetsch (US'999). The US patent describes very similar compounds to that claimed herein for a variety of pharmaceutical uses as discussed in col. 1. While closest compound in col.12, lines 17-18 does not anticipate the instant scope, it is an obvious variant being an adjacent homolog of that claimed herein-i.e. having ethylene vs. methylene link corresponding to instant L. Note that Poetsch also teaches varying chain lengths as can be seen in the "A" definition therein. This includes C1-C4 alkylenes. See col.3, lines 38-46. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify the ethylene compound pointed out above by changing the chain link and in so doing obtain an instant compound with the expectation that it too will possess one or more uses taught by the applied art.

EP'053 which is discussed by applicants in the specification has been noted. It is agreed that the invention is directed to pyrazoles in which the

phenyl and piperazine group are not on adjacent ring positions. The examiner will inform CAS of the error in structural assignment.

Claim 15 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Species in this claim contain substituents at either phenyl or pyrazole not particularly suggested by Gerlach.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

E Bernhardt

Emily Bernhardt
Primary Examiner
Art Unit 1624